Cutaneous Head and Neck Cancers in the High-Risk Immunosuppressed Population

Karen Y. Choi, MD[a,1], Cecelia E. Schmalbach, MD, MSc[b,*]

KEYWORDS

• Immunosuppression • Solid organ transplant • Cutaneous carcinoma
• Head and neck • Nonmelanoma skin cancer • Melanoma of the head and neck

KEY POINTS

- The immunosuppressed patient population is a uniquely high-risk group for aggressive cutaneous malignancies with worse outcomes.
- Rates of keratinocyte carcinomas, malignant melanoma, Merkel cell carcinoma, and Kaposi sarcoma are higher in the immunosuppressed patient cohort.
- The American Joint Committee on Cancer eighth edition cancer staging now acknowledges the poorer prognosis of cutaneous squamous cell carcinoma in the immunosuppressed population, but further studies are warranted to reconcile the heterogeneous data in order to fully delineate the impact of immune status on prognosis.
- Clinical trials for immunotherapy do not include the immunosuppressed population, and special considerations as well as close communication with the multidisciplinary transplant team is paramount when considering systemic therapy in this patient population.

INTRODUCTION

The immunosuppressed (IS) population encompasses a diverse cohort of patients to include iatrogenically immunocompromised organ transplant recipients (OTRs) as well as patients with chronic lymphoid malignancies, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), and autoimmune disorders. Cutaneous cancers in this high-risk patient group are clinically distinct from the general immunocompetent population, showing aggressive behavior with associated poor outcomes.[1,2] This article reviews the pathogenesis, epidemiology, incidence,

[a] Department of Otolaryngology Head and Neck Surgery, The Pennsylvania State University, College of Medicine, Hershey, PA, USA; [b] Department of Otolaryngology Head and Neck Surgery, Lewis Katz School of Medicine, Temple University, 3440 North Broad Street, Kresge West 309, Philadelphia, PA 19140, USA
[1] Present address: 500 University Drive, MCHO91, Hershey, PA 17033.
* Corresponding author.
E-mail address: cecelia.schmalbach@tuhs.temple.edu

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prognosis, and special considerations required in managing cutaneous cancers in the IS patient population.

PATHOGENESIS

The skin serves as a mechanical barrier of protection. In addition it is widely accepted as a peripheral immunologic organ, housing many of the critical lymphoid organ cells to include dendritic antigen presenting cells and Langerhans cells commonly associated with the spleen, lymph nodes, and Waldeyer ring.[1,3,4] The dendritic cells housed in the epidermis and dermis are capable of inducing primary immune responses by presenting antigens encountered on the skin to T cells.[1,5]

The exact pathogenesis of cutaneous malignancies in the IS population is multifactorial. It is generally accepted that the major cause is the combination of ultraviolet (UV) radiation exposure with reduced immune surveillance secondary to the chronic immunosuppressive medications.[6–8] In addition, IS patients are more susceptible to oncogenic viruses such as Epstein-Barr virus, human papillomavirus (HPV),[8,9] Kaposi sarcoma herpesvirus or human herpesvirus 8 (HHV8), human T-cell leukemia virus type 1 (HTLV-1), and Merkel cell polyomavirus.[10,11]

INCIDENCE AND PROGNOSIS

Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (cSCC) is one of the most common malignancies following transplant.[12–14] As immunosuppressive regimens improve, patients are surviving longer.[6] This prolonged chronic immunosuppression increases the risk of de novo secondary cancers, the most common being cutaneous malignancies.[6,8,15] OTRs on chronic immunosuppression carry a 65-fold to 100-fold increase in cSCC compared with the general population; patients with chronic lymphoid malignancies carry an 8-fold to 13-fold increase in incidence.[2,6,16–22] Increased rates of cSCC are also found in other immunosuppressed patients, such as those with lymphoma and HIV.[23,24]

Overall, cSCC portends an excellent prognosis, with 5-year survival rates exceeding 90% in the general population. However, IS patients experience a more aggressive histology[12,25–27] and associated worse outcomes,[2,19,28,29] with recurrence rates reaching 7.2 times that of the general population.[25] Although cSCC metastasizes to regional lymph nodes or distant sites in 2% to 5% of the general population,[30,31] immunosuppression is recognized as an independent risk factor for regional metastasis,[31] with rates reaching 22.5%.[6,32–34] Similarly, locoregional recurrence (LRR) and distant metastasis are rare in the general population (13%–48% and 7%–19%, respectively).[2,22,35,36] However, immunosuppression is an independent prognostic factor for LRR as well, with increased risk ranging from 2.66 to 3.79 times higher than the general population.[37,38] Recurrence-free survival is significantly lower in the IS population, with rates of 47.3% versus 86.1% for immunocompetent patients, as well as lower locoregional progression-free survival rates at 38.7% versus 71.6% at 2 years.[2]

Ultimately, cSCC represents a significant cause of mortality in the IS population, with a decreased overall survival (OS) rate of 66% at 5 years and 43% at 10 years compared with the general population.[12,14,18,39–42] One retrospective cohort study found immunosuppressed patients had a significantly lower disease-specific survival (DSS) at 3 (75.8%), 5 (68.2%), and 10 years (62.4%) compared with the immunocompetent cohort (87.1%, 84.1%, 83.2%, respectively).[43]

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cutaneous cancer overall and, similar to cSCC, has an increased incidence among OTRs. Together, BCC and cSCC develop in 40% of OTRs within 20 years after transplant, with 75% of patients diagnosed within 1 year.[16,44,45] The incidence ratio of BCC to cSCC among the general population is roughly 4:1, but this ratio is reversed in the IS population,[8,46,47] with OTRs 20 times more likely to develop cSCC than BCC.[8,15,20,48] However, the incidence of BCC in the IS population remains increased with respect to the general population, with a 10-fold higher risk.[12–14,49,50] Note that BCCs in the OTR population often develop in sun-protected areas and other unusual locations not typical of the general population, such as the external auditory canal, genitalia, hand, wrist, and axilla.[44]

Cutaneous Melanoma

Similar to cutaneous squamous cell carcinoma (SCC), IS patients are at higher risk of developing malignant melanoma, with rates 2-fold to 4-fold higher in OTRs compared with the general population.[20,51–57] Similarly, patients with HIV/AIDS are noted to have 2.6-fold increased risk of developing melanoma,[50,58,59] and patients with chronic lymphocytic leukemia (CLL) have an increased risk between 2.8-fold and 6.2-fold.[50,60–64]

Given the strong immunogenicity of melanoma biology, it is not surprising that melanoma in the setting of immunosuppression has a more aggressive course and worse prognoses.[65–67] OTRs have been shown to have a 3-fold higher risk of melanoma-specific mortality.[51,65,68,69] OS for OTRs with melanoma is significantly lower than that of the general population, with 2-year, 5-year, and 10-year rates reported to be 77%, 54.2%, and 40.6% respectively, compared with the general population rates of 95.6%, 82.1%, and 75.2%.[67] As expected, melanomas thicker than 2 mm had significantly worse OS, with a hazard ratio of 11.49 compared with the general population.[67,70,71] However, thinner melanomas (<1 mm) were also still noted to have an increased risk of mortality, with an HR 4.74 compared with the general population.[51] Differences in survival were not noted based on donor organ.[65]

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine malignancy associated with the Merkel cell polyomavirus.[10] Overall, IS patients who develop MCC tend to be younger and have a more aggressive behavior pattern leading to lower MCC-specific survival and OS in this population.[10,66,72–74] OTRs are at greater risk (10-fold to 24-fold) of developing MCC compared with the general population.[10,75–77] The incidence of MCC in the OTR population is associated with increased age at time of transplant, with more than 70% of cases occurring in patients more than 50 years old at time of transplant, and with increased duration of immunosuppression.[75] Increased incidences have also been shown in other immunodeficient states, including UV-induced immunosuppression, hematologic malignancies, HIV/AIDS, and autoimmune diseases.[10,78–81]

MCCs in the IS population is associated with a 12-fold increased risk of MCC-specific death in the OTR population.[10,73] Higher levels of intratumoral infiltrating lymphocytes were found to be an independent predictor of improved outcomes, showing the importance of an intact immune response in MCC.[82,83]

Kaposi Sarcoma

Kaposi sarcoma (KS) is an endothelial tumor caused by human herpesvirus 8 (HHV-8) infection and closely associated with immunosuppression, especially in HIV/AIDS,

where it is often the first presentation of this disease.[20,52,84,85] Before the AIDS epidemic of the 1980s, rates of KS were extremely low, with an incidence in the United States of 0.2 per 100,000 person years.[86] This incidence increased to 200,000 among patients with AIDS compared with the general population.[87] KS also occurs at higher rates among OTRs, where it is diagnosed 200 times more often than the general population.[88] It develops quickly after transplant, with a mean time to diagnosis of 13 months.[6] Nonwhite men receiving lung transplants are at greater risk, as are patients of Mediterranean, Jewish, Arabic, Caribbean, or African descent.[6,84]

RISK FACTORS UNIQUE TO THE IMMUNOSUPPRESSED POPULATION

A host of risk factors in the IS population place them at greater risk of developing cutaneous malignancies. Similar to the general population, exposure to UV radiation remains an important factor, as does a prior history of skin cancer.[6] In addition, patient demographics play a role in developing posttransplant cSCC. Multiple studies have shown that white transplant recipients with Fitzpatrick scale of 1 to 3 were at highest risk of skin cancer.[46,89–99] Men were 3 times more likely to develop posttransplant skin cancer compared with women.[99]

Numerous studies found that patients with a history of pretransplant cSCC carry a high risk of developing cSCC posttransplant, and multiple multivariate models showed this to be the single strongest predictor of skin cancer risk.[100] The presence of actinic keratoses and viral warts around the time of transplant was also associated with increased risk of skin cancer.[101] Several observational studies suggested that lung, heart, and combined pancreas-kidney transplant patients were at higher risk than kidney and liver transplant recipients.[56,102,103] Patients who underwent transplant at an older age were also found to be at increased risk of developing cSCC sooner after transplant, with a median time from transplant to first cSCC of 3 years for patients more than 60 years old compared with 13 years for patients 18 to 40 years of age.[97,104]

Several risk factors have been associated with development of melanoma after OTR, including male gender and increased age at time of transplant.[51,105] In a comparison of the different types of solid organ transplants, patients who underwent liver or lung transplants were noted to have lower risk of developing melanoma compared with patients who received kidney transplants.[51] Vajdic and colleagues[52] also found that the intensity and duration of immunosuppression were further important determinations in the development of melanoma in OTR. Cases of transmission of melanoma from organ donors to recipients have been reported. In a study analyzing 104 donor-transmitted malignancies, melanoma was found to be the second most frequently transmitted malignancy, following renal cancer.[106] The exact mechanism of how this occurs is unknown, but it is hypothesized to be intricately involved with the tumor biology of melanoma.[50,107]

The connection between immunosuppressive medications and MCC was first reported by Penn and First[72] in 1999 after noting the increased aggressiveness of MCC compared with the general population and the appearance in younger patients (mean age of 53 years).[72,78] Clarke and colleagues[75] reviewed the US Scientific Registry of Transplant Recipients and noted that the risk of developing MCC was highest in older patients, with more than 70% of cases occurring in patients more than 50 years old at the time of transplant, and was more common in men (70% higher incidence), with 5 times higher risk in white compared with nonwhite recipients.

The role of HPV infection in the development of cSCC has been hypothesized.[8,108] Several studies showed increased frequency of HPV DNA in cSCC tumors compared with nonmalignant, normal skin of IS patients (90% vs 11%–32%).[9] One study showed

this link to be unique to cSCC and found no similar association between HPV and BCC.[108] It remains unclear whether the high-risk alpha-HPV types versus the low-risk beta-HPV types play a more prevalent role in the carcinogenesis of these skin tumors,[109–111] and further study is required.

STAGING

American Joint Committee on Cancer

At present the American Joint Committee on Cancer (AJCC) provides cancer staging for cutaneous melanoma,[112] MCC,[113] BCC, and cSCC.[114] cSCC warrants special comment given the recent implementation of the eighth edition of AJCC staging, which specifically mentions the IS patient population.

The overall excellent prognosis of cSCC coupled with the lack of a dedicated, national registry makes accurate staging more challenging compared with cutaneous melanoma. Given these challenges and the propensity for cSCC to develop in the sun-exposed region of the head and neck (HN), the latest staging iteration was developed by a panel of HN experts and applies to this specific anatomic region.[114]

The new system remains founded on the traditional tumor-nodal-metastasis categories. Specifically, the tumor stage is based on the cancer diameter as well as invasion into surrounding structures, to include perineural and bone. Similar to other HN cancers, the nodal stage is based on number of metastatic nodes, nodal size, and the presence of extranodal extension. The metastatic stage is defined by the presence (M1) or absence (M0) of distant disease.

The designers of the staging system acknowledge that immunocompromised OTRs are more prone to cSCC and have a worse prognosis with respect to recurrence and survival.[114] Although strong consideration was given to incorporating immune status into this latest staging system, the literature was deemed conflicting and limited to small cohort studies. The panel identified only 1 supporting multivariate study comprising 31 IS patients, to include HN, trunk, and extremity. Therefore, immune status was not formally incorporated into the system but centers collecting data for prospective study are encouraged to denote immune status.

In order to address the heterogeneous nature of prior studies and the small cohort sizes, Elghouche and colleagues[12] recently conducted a systematic review of the literature with meta-analysis to specifically investigate the impact of immunosuppression on HN cSCC. The investigators identified 317 IS HN patients in 17 studies. Immunosuppression was found to have a statistically significant worse prognosis with respect to LRR (HR 2.20), DFS (HR 2.69), DSS (HR 3.61), and OS (HR 2.09).

Sentinel Node Biopsy

Because immunosuppression has been found to be an independent risk factor for developing metastatic disease,[31] with regional metastasis rate ranging between 2.2% and 21%,[32,115–117] increased consideration may be warranted for use of sentinel lymph node biopsy (SLNB) for nodal staging in the high-risk IS patient population.

SLNB provides a minimally invasive means for pathologic staging.[118] HN SLNB has been shown to be safe and reliable, with a false rate of omission (failure in a previously mapped regional nodal basin deemed negative for metastatic disease) of 4.7%, which mirrors that of cutaneous melanoma, where the technique is accepted as standard of care.[119] Current cSCC NCCN guidelines recommend consideration of SLNB for high-risk, localized tumors, which includes the IS population.[120] At present, SLNB remains only as a staging modality for cSCC, and the impact on survival remains unknown.

CUTANEOUS CANCER TREATMENT OF IMMUNOSUPPRESSED PATIENTS

Treatment recommendations for cutaneous malignancies in the IS population are based on tumor stage and mirror those of the general population.[120–125] However, some unique considerations do warrant further discussion.

Reduction in Immunosuppression

Treatment of cutaneous malignancies in the iatrogenically IS patient population should include close partnership with the multidisciplinary transplant team to safely reduce immunosuppression when possible. When considering reduction or modulation of immunosuppressive therapy, discussion with the patient's transplant team is paramount to ensure a safe balance between potential organ rejection, risk of development of skin cancers, as well as the psychological impact to the patient. Although specific guidelines have not been established, 1 expert consensus survey made recommendations on the level of immunosuppression based on type of solid organ transplant and skin cancer history.[126] Reduction should be considered in patients who have developed numerous cutaneous malignancies or those who develop recurrent or metastatic disease.[6,93,126,127]

One study of 231 transplant patients identified increased acute rejection rates in the setting of lower-dose immunosuppressive therapy (cyclosporine and azathioprine); however, overall graft survival rates were similar and patients experienced fewer cSCCs and BCCs (14.7% vs 22.6%).[128] In addition, numerous studies have shown decreased incidence of cutaneous malignancies with the use of mycophenolate mofetil (MMF) compared with azathioprine,[129,130] and mammalian target of rapamycin (mTOR) inhibitor use such as sirolimus or everolimus rather than calcineurin inhibitors.[131–135]

Although reduction of immunosuppression has been shown to decrease incidences of melanoma,[51] reduction may not be feasible for lifesaving organ transplants. As such, there has been much discussion surrounding safe use of systemic agents in this population. There are no specific guidelines for treatment of MCC in the IS population, and surgical excision with adjuvant radiation as indicated remains the standard of care in this cohort.[136] Some reports support temporary or partial regression of MCC in patients who had reduction of their immunosuppressive regimens; however, because of the overall rarity of this disease, generalized recommendations based on these data are limited.[137,138] If feasible, reducing immunosuppression to the lowest level possible without risking graft rejection is recommended.[126]

Targeted Immunotherapy

Surgical management with adjuvant therapy based on final pathology remains the standard of care for cutaneous malignancies in the IS population.[120–123] However, special consideration is required in the use of systemic immunotherapy. Ideally the treatment plan is formalized in the setting of a multidisciplinary tumor board well versed in the treatment of advanced cutaneous cancers.

Cemiplimab is a monoclonal antibody against programmed death 1 (PD-1). It was approved by the US Food and Drug Administration (FDA) for use in advanced and metastatic cSCC following results from a phase I/II trial published in 2018 showing response rates of 47% to 50% and durable disease control rates of 61% to 65%.[139] More recently, pembrolizumab received similar FDA approval.[140] Note that these trials did not include the IS population.[15] The PD-1 signaling pathway is thought to play an important role in pathogenesis of organ rejection[141]; thus, the use of anti–PD-1 inhibitors must be considered with extreme caution in OTRs and they are

traditionally considered contraindicated in this high-risk patient population. One retrospective review at a US cancer center reported their experience treating 39 OTRs with checkpoint blockade, showing a 41% rate of allograft rejection with median time to rejection of 21 days and a total graft loss in 81% despite aggressive treatment with high-dose corticosteroids and/or sirolimus, tacrolimus, MMF, or intravenous immunoglobulin.[142] Furthermore, they showed a mortality of 46% in patients, related to allograft rejection or rejection complications.[142] Similarly, 1 case series reported increased mortality associated with cetuximab (anti–epidermal growth factor antibody) use in 2 lung transplant recipients secondary to diffuse alveolar hemorrhage, suggesting caution with use in this population.[143]

Ipilimumab is a CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) checkpoint inhibitor that may be better tolerated than PD-1 inhibition. However, graft rejection has been reported with both medications.[144–146] Although several case reports have been published showing tolerance of ipilimumab in transplant patients, including 2 kidney transplants and 1 liver transplant,[146,147] further investigation is required.

Multiple clinical trials are underway to specifically explore the efficacy and safety of checkpoint blockade in OTRs, including an Australian trial evaluating nivolumab in the renal transplant population for treatment of cSCC (ACTRN12617000741381) and a US trial evaluating the effect of tacrolimus and prednisolone immunosuppression with nivolumab and ipilimumab in renal transplant recipients (NCT03816332).[141] Results from these studies will be extremely important in showing the objective clinical response in this vulnerable patient population and true rates of organ rejection.

It is worth noting that patients with CLL and autoimmune disorders are also often excluded from most clinical trial investigations using checkpoint blockade.[141] At present, knowledge surrounding the feasibility of checkpoint blockade in these populations is limited to small cohort studies. One retrospective study involving 3 with CLL treated with PD-L1 reported a 62% rate of objective response at median follow-up time of 16.5 months, and a 12-month progression-free survival of 68.4%.[148] Another case-control study evaluating response rates of checkpoint blockade in the setting of melanoma and CLL showed promising results similar to the Keynote 629 trial,[149] and further studies are investigating outcomes of checkpoint blockade with CLL in combination with other agents.[141] In patients with autoimmune diseases, off-label treatment with checkpoint inhibitors has suggested these patients may be treated; however, only under close and strict supervision because rates of exacerbation requiring immunosuppression are documented to be 2 to 3 times higher than in the general population. A higher rate of significant autoimmune toxicities has also been observed.[150]

Kaposi Sarcoma

The primary treatment of KS is to reduce the level of immunosuppression[93,151] or to bolster the immune system by initiating medications such as antiretroviral therapy (ART) in the case of AIDS-induced KS.[85] KS regression has been documented after altering immunosuppressive medications from cyclosporine as well as tacrolimus to sirolimus in renal transplant patients.[152–158] The introduction of ART dramatically decreased the incidence of AIDS-related KS[157] and treatment of HIV with ART may cause regression of some tumors, with up to 80% of early-stage disease managed by initiation of ART.[158]

PREVENTION

Mitigating risks is extremely important for high-risk IS patients. They should be counseled on sun avoidance, use of sunscreen, and the importance of sun-protective

clothing. Before proceeding with organ transplant, dermatology consultation is strongly recommended for screening and treatment of any cutaneous malignancies or precursor lesions.[159,160] Depending on cancer type and stage, patients with a history of skin cancer may be advised to undergo a period of observation before proceeding with transplant.[160] For low-risk keratinocyte carcinomas, melanoma in situ, or lentigo melanoma, it is acceptable to proceed with transplant with frequent whole-body skin examinations. However, for patients with high-risk cSCC, MCC, or malignant melanoma, the general recommendation is to wait 2 to 5 years before transplant.[160]

It is imperative that IS patients undergo routine whole-body skin examination to evaluate for development of new cutaneous malignancies. One Canadian study followed more than 10,000 OTRs for more than 5 years and found that routine skin examination was associated with a 34% decrease in the development of advanced nonmelanoma skin cancers.[161] As noted earlier, partnership with the multidisciplinary transplant team is also imperative in reducing immunosuppressive therapy as safely as possible to avoid both recurrence and new cutaneous cancers.

SUMMARY

Immunosuppressed patients carry an increased risk of cutaneous malignancies, especially for cSCC among organ transplant patients. Although skin cancers traditionally portend an excellent prognosis, they are known to be aggressive with worse outcomes in this high-risk group. Diligent surveillance that includes patient education and early intervention is imperative to reduce the risk associated with skin cancer development. Treatment planning for patients with advanced cutaneous malignancies in the setting of immunosuppression ideally transpires in the setting of a multidisciplinary oncology team well versed in cutaneous cancers. In addition, treatment in the iatrogenically IS patient population necessitates close partnership with the multidisciplinary care team to safely reduce immunosuppression whenever possible.

DISCLOSURE

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